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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,550	CHAUDRY, IMTIAZ	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,10-12,22-25,27-30,35 and 71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-6, 10-12, 22-25, 27-30, 35, and 71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/16/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-6, 10-12, 22-25, 27-30, 35, and 71-77 are pending. Applicant previously cancelled claims 2-3, 7-9, 14-21, 26, and 31-34, and 36-70. Applicant has newly cancelled claim 13. Applicant has amended claims 1, 4, and 75. Claim 77 is new. Receipt and consideration of Applicant's new IDS's (submitted 7/16/10; 5/7/10; and 3/31/10), amended claim set, terminal disclaimer, and remarks/arguments submitted on June 29, 2010 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments. Applicant's claim amendments have necessitated a new rejection under 35 U.S.C. § 112, 1st paragraph and rejection of new claim 77 under § 103(a), as set forth below.

Election/Restrictions

The election/restriction of record remains proper and is maintained at this time.

Terminal Disclaimer(s)

The terminal disclaimer filed on June 29, 2010 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Application No. 11/931,484 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant amended claim 12 to recite, "0.05% by weight of suspended solid fluticasone particles." Applicant's remarks do not cite any page where support for the claim amendment can allegedly be found, but merely state that no new matter has been introduced. A search of the specification did not uncover any support for the composition having fluticasone particles in an amount of 0.05% w/w. Thus, the amendment to claim 12 introduces new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281).

Applicant Claims

Applicant claims an aqueous formulation comprising (a) 0.04% to 0.06% w/w of a suspended steroidal anti-inflammatory that is fluticasone or a pharmaceutically acceptable salt, ester, enol, ether, enol ether, enol ester, acid, or base thereof characterized by the particle size distribution described in claim 1, (b) an antifungal agent (e.g. amphotericin beta), further comprising (c) a preservative, such as benzalkonium chloride (e.g. claims 23-24 and 28), (d) other excipients (e.g. dextrose, carboxymethylcellulose sodium, etc.), and (e) an antibiotic (claims 29-30), wherein the formulation is suitable for administration to the para-nasal mucosa.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, the DIH, ad Osbakken are restated herein below.

FLONASE® is a commercially available nasal spray sold in a metering, atomizing, spray pump containing therein an aqueous suspension of suspended microfine fluticasone propionate (16 g bottle delivering 120 individual 50 microgram doses per actuation; i.e. **0.0375% w/w fluticasone propionate**), **microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, 0.25% w/w phenylethyl alcohol, wherein the aqueous suspension has a pH between 5 and 7** (PDR printout, pg. 1, "Description section"). The recommended dosage of FLONASE® for adults is 50 micrograms per nostril for a total **daily dosage of 200 micrograms**. Alternatively, the administration of two 100 microgram doses twice daily is also effective. Adolescents and children 4 years of age and older should begin with **100 microgram dosages** (1 spray per nostril per day), but may use 200 micrograms (2 sprays per nostril per day) if not adequately responding (PDR, pg. 7, "Dosage and Administration" section).

The DIH demonstrates that FLONASE® was a commercially available product at least as early as 1999. The DIH also sets forth that **neomycin sulfate** (pg. 721-722) was a known antibiotic at the time of Applicant's invention and that **acyclovir** (pgs. 26-28), **ganiciclovir** (pgs. 463-464), **foscarnet** (pgs. 454-456), **cidofovir** (pgs. 225-226), and **formivirsen** (pgs. 453-454) were all known antiviral agents at the time of Applicant's invention.

Bernini teaches a process for the preparation of suspensions of drug particles for **inhalation delivery**, providing **optimized particle size and distribution**. A further aspect of the invention is directed to a process for preparing micronized **sterile steroidal formulations** by gamma-irradiation (abstract; col. 1, lines 17-27; col. 4, lines 14-25).

Bernini teaches that a number of **inhalation formulations** have been marketed for some years for the administration of **steroidal anti-inflammatory agents** for the topical **treatment of rhinitis and/or sinusitis**. An example of these steroidal anti-inflammatory drugs includes **beclomethasone dipropionate** (BDP). These formulations can be administered in the form of a finely divided (i.e. micronized powder) **suspension in an aqueous phase** containing necessary surfactants (i.e. emulsifiers) and/or cosolvents. When intended for administration in the form of **metered dose aerosol sprays**, these sprays should also contain **a low-boiling propellant** (col. 1, lines 8-12, 17-20, and 22-26).

Bernini teaches that in the process of preparing her formulations an **aqueous solution**, which constituted the carrier optionally, contains **wetting agents, surfactants** (i.e. emulsifiers), **preservatives, stabilizing agents, buffers**, and can optionally be **sterilized**.

Bernini teaches that the degree of solid particle size reduction and the resulting particle size distribution of the formulations produced by her process can be optimized by controlling several variables: (i) the type and size of the interaction chamber; (ii) the operating pressure; and (iii) the processing time and the number of cycles the material passed through. The process effects are also dependent on the physicochemical properties of the ingredients subjected to treatment, however pressure and process times can be modified to achieve the desired results (col. 2, lines 33-43).

Bernini teaches that it would be highly advantageous to provide aqueous suspensions of steroids to be delivered in single unit-dose preparations, because **sterility** is a requirement in greater demand for pharmaceutical formulations intended for **nebulization** (col. 4, lines 31-36).

Bernini teaches that BDP micronized formulations when subjected to gamma radiation at 2 to 9 KGy remain chemically stable (col. 5, lines 53-55). Bernini states that the invented method allows for the preparation of sterile micronized BDP suspensions (col. 6, lines 19-21). Other drugs, which can be used in Bernini's formulations and methods, include corticoid steroids, such as **fluticasone propionate**, and other inhalable anti-inflammatory steroids (col. 1, lines 17-27; col. 4, lines 14-25; claims 1, 2, and 5-6).

Bernini teaches that the BDP starting material used in her process has a particle size of less than 10 microns, **preferably less than 5 microns**. The formulations for inhalation resulting from her invented process can be used to treat any **allergic** and/or inflammatory **condition of the nose** or the lungs (col. 6, lines 33-43).

Harris teaches **an aqueous nebulizer suspension formulation of mometasone furoate monohydrate**, which also comprises a nonionic surfactant, soluble salt, and optionally a pH buffer (title; abstract; claims 1-15), wherein the suspended **solid mometasone particles have an average particle size of less than about 5 microns** (claim 14; pg. 4, lines 14-16) **or less than about 2 microns** (claim 15; page 4, lines 14-17). Mometasone furoate is a well-known anti-inflammatory steroid. Harris teaches that the formulations can be obtained in sterile form **by preparation under sterile conditions** (pg. 9, lines 17-19) and, alternatively, in lieu of sterilization a preservative may be incorporated into the formulations (pg. 4, lines 21-25). Harris

teaches that sterilization by filtration is not feasible for a suspension formulation and that sterilization by gamma radiation or heating induces mometasone degradation (pg. 9, lines 8-15).

Harris teaches that the preferred micronization technique **is jet milling and that this technique may be used *to reproducibly obtain desired distributions* of micron and submicron sized particle**s (pg. 10, lines 5-7).

Harris teaches that inhaled therapeutics are typically used to treat airway disorders, including asthma, **infections**, and **various inflammatory conditions** (pg. 1, lines 18-20).

Osbakken teaches **pharmaceutical compositions** are described that comprise one or more active ingredients including an **anti-infective agent, anti-inflammatory agent, and antibiotic combinations** or combinations of others of these classes of ingredients, especially compositions **formulated as a solution or suspension** in a unit dose for aerosol administration to treat chronic sinusitis (abstract).

Osbakken teaches that sinusitis is an inflammation of the membrane lining one or more **paranasal sinuses (i.e. paranasal mucosa)**, and there are three principle kinds of sinusitis: acute, recurrent acute, and chronic [0004]. Therefore, it is obvious that the term rhinosinusitis encompasses sinusitis as in a genus-species relationship, wherein sinusitis is a species of the genus rhinosinusitis. Species are obvious over the genius.

Osbakken teaches that bacteria commonly associated with acute sinusitis, and that, although less common fungal sinusitis does occur and is often associated with infections caused *by Aspergillus, Vurvularia, Bipolaris, Exserohilum, Metarrhizium anisopliae,* and *Mucormycosis* fungi [0007]-[0008]. The primary objectives for the treatment of sinusitis are reduction of swelling, eradication of infection, draining of the sinuses, and ensuring that the sinuses remain

open [0015]. Nebulization therapy is a conventional treatment for pulmonary infections and is also known to have been **used for sinus infections**, with few systemic side effects [0026].

Osbakken teaches that it had been suggested previously in the prior art to use small **aerosol particles of about 2-4 microns** in the treatment of sinusitis. See paragraphs [0027]-[0029], especially [0029].

Osbakken teaches that the use of synergistic antibiotic combination is desirable; because it allows for the treatment of more difficult infections (e.g. infections due to multiple-antibiotic-resistant organisms) and lower dosages, thereby reducing the probability of toxicity complications, treatment time, and therapy cost. For example, **cefuroxime and gentamicin**, either individually or in combination with other agents, have been used to treat patients with sinusitis [0066]-[0068].

Osbakken teaches that his invention involves the **topical delivery of medications to the nasal cavity and sinuses** by aerosolizing **aqueous solutions or suspensions** of the medications taught. The aerosolized anti-infective particles are surprisingly effective when they have a mass median aerodynamic diameter (MMAD) of about 1.0 to 5.0 microns [0081]. Aerosolization/atomization of the formulations for nasal inhalation by a patient will result in liquid aerosol cloud particles having a MMAD of preferably between **about 0.5 microns and 10 microns**. Examples of suitable medicaments include **amphotericin beta (anti-fungal), cefuroxime (antibiotic), ciprofloxacin (antibiotic), tobramycin (antibiotic), cefoperazone (antibiotic), erythromycin (antibiotic), gentamycin (antibiotic)** [0085], **fluticasone (anti-inflammatory), and beclomethasone (anti-inflammatory)** [0139]. An exemplary formulation is described in [0178] and comprises **amphotericin beta (10 mg unit dose)**, hydrocortisone

sodium succinate (50 mg dose in 3 ml sterile water) together with an anti-inflammatory agent. **Preferable dosage ranges** of various active agents including **amphotericin beta, beclomethasone, fluticasone, fluconazole, itraconazole, aztreonam, cefepime, doxycycline, tobramycin, vancomycin**, etc. are taught in Table-1.

Osbakken teaches that if necessary, osmotic pressure may then be raised to fall within a preferred range **by adding NaCl, dextrose, or other salts** to the liquid [0096]. Surfactants can be used as dispersing agents, solubilizing agents, and spreading agents. Some examples of surfactants are: PEG 400, sodium lauryl sulfate, spans (20-40-60 etc), tweens (**polysorbates, 20-40-60 etc**), tyloxapol, propylene glycol, and **benzalkonium chloride**. Benzalkonium chloride is also a preservative.

Osbakken teaches in [0104] a general preparation of his invented formulations, wherein after determining the medications to be used in the formulation, each ingredient is weighed/measured individually, added together, mixed with diluent (e.g. **sterile water**), filtered with a coarse filter, and then a fine filter (5 micron, 2 micron, 1 micron, 0.45 micron, or 0.22 micron). The preparation is tested to ensure it is within the established parameters for surface tension, osmolarity, pH, and sodium chloride equivalency. To prepare a unit dose, the ingredients of such formulations generally will be dissolved in a solvent such as water or saline solution, in a volume between about 0.5 and 6.0 ml.

Osbakken teaches a **method of treating a mammal suspected or diagnosed as having chronic sinusitis** comprising the step of **administering** to the patient the pharmaceutical composition of any one of claims 1 or 2, by aerosolization using a nebulizer, which delivers aerosol particles of between about 1 to 5 microns in average diameter in claim 16 of US-2002.

Osbakken also teaches in [0235] that **the medication is nebulized three times daily** and that the therapeutic treatment was continued for a total of seven days.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

The product information concerning FLONASE® is silent as to the particle size distribution of suspended beclomethasone. The product size distribution rendered obvious by the teachings of Bernini as further articulated below. FLONASE® lacks the teaching of compositions further comprising an antifungal agent or an antibiotic. This deficiency is cured by the teachings of Osbakken, which has been provided as a supporting document to show what was known in the art regarding the treatment of rhinitis/sinusitis. Harris is provided as a supporting reference to demonstrate particle sizes recognized in the art as being suitable for nasal administration and that it is conventional to optimize particle size distributions.

Finding of Prima Facie Obviousness Rational and Motivation *(MPEP §2142-2143)*

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the compositions of FLONASE®/Bernini with the teachings of Osbakken, because it was well-known at the time of the instant invention that sinusitis is a species of rhinosinusitis (i.e. rhinitis) and is characterized by inflammation of one or more membranes of the paranasal sinuses (i.e. paranasal mucosae) that can be caused by microbial infection (i.e. fungal or bacterial infection). Using what was readily known to the ordinary skilled artisan at the time of the instant invention, an ordinary skilled artisan would have

recognized that the underlying cause of sinusitis or rhinitis could be treated by the inclusion of an anti-microbial agent, such as an anti-fungal agent (e.g. amphotericin beta) or an antibacterial (e.g. doxycycline) in a therapeutically effective dosage. Thus, despite the fact that Osbakken focuses its teachings on aqueous solutions that are filtered, an ordinary skilled artisan would nonetheless have been motivated to modify FLONASE® to incorporate a therapeutically effective amount of an anti-fungal agent and/or an antibacterial to obtain a composition suitable for treating not only the inflammation resulting from an infection, but also suitable for treating the underlying cause of the inflammation (i.e. a fungal and/or bacterial infection). An ordinary skilled artisan would have had a reasonable expectation of success upon modification of the FLONASE®/Bernini composition to further comprise an anti-fungal or antibacterial agent because these are art-recognized therapeutics for treating fungal and bacterial infections and are known in combination with anti-inflammatory steroids.

Regarding Applicants' data it is clear that the performance of both high and low-dose FLONASE® vis-à-vis the high and low dose formulations of Applicants' invention result in clinically comparable and in some cases indistinguishable results (see for example data points in Applicants' figure 1 at days 7, 10, and 12-14). Applicant has asserted that the claimed particle size distribution results are unexpected. The difference between the low dose and high dose data is that the high dose data is associated with two dosing events of either FLONASE® or Applicant's formulation. It is noted that Applicant's data is limited to formulations comprising 0.050% w/w fluticasone (see Table 3 on page 30 of the specification of copending 10/414,682 incorporated by reference into the instant application).

Applicants' "quantified" subjective data is graphically presented in Figures 1-4 of copending application 10/414,682 has been considered by the Examiner. It is the Examiner's position that the data presented does not demonstrate unexpected results when compared to the prior art data (FLONASE®). The Applicants' data compared to FLONASE® exhibit the same pattern of fluctuations over a period of 2-14 days; is of a similar magnitude, and in several instances is the same (see, for example, data points at days 4, 5, 9, and 10). It is also noted that the data points are not displayed with error bars. The display of the uncertainty in the data points is deemed necessary because the data reported in Figures 1-4 are based upon a least squares mean analysis of the raw Total Nasal Symptom Scores (TNSS) (i.e. these are aggregate data), which are subjective data assigned values by patients on an arbitrary scale of 0 to 3, where 0 means no symptoms and 3 means "severe symptoms present," wherein these subjective data were manipulated using the ANOVA model. For this reason, wherein Applicants' subjective data for the invented compositions and the prior art data points are very similar in magnitude, it would be reasonable for one to conclude that these data points are the same within a margin of error. Furthermore, the general differences depicted in the Figures are merely a difference of degree at best and not a difference of kind. A difference of degree is not sufficient to support patentability. The difference between the low dose and high dose data is that the high dose data is associated with two dosing events of either FLONASE® or Applicant's formulation. It is noted that Applicant's data is limited to formulations comprising 0.050% w/w fluticasone (see Table 3 on page 30 of the specification of copending 10/414,682 incorporated by reference into the instant application). Contrary to Applicant's statements, Applicant's results when taken as a whole and compared to the results exhibited by FLONASE® are not considered to demonstrate

anything surprising or unexpected, as has been explained in previous office actions. Thus, Applicant's formulations are not considered to exhibit unexpected or surprising results either.

Regarding the recited particle size distribution, it has already been established that optimization of particle sizes is routine in the field of inhalable formulations (i.e. both oral and nasally administered) (Harris). Thus, finding the optimal particle size and particle size distribution for a given particulate formulation is routinely practiced in the art and as applied to the combined prior art, would reasonably be expected to yield the same or a substantially similar particle size distribution as claimed by Applicants.

Regarding the recited stability, Applicant is correct that the combined prior art is silent with regards to the stability as recited in Applicant's claims. However, it is concluded that the recited stability is a consequence of the claimed formulations being sterile, as evidenced by the statements in paragraph [0061] of the PG-PUB of Applicant's specification that the formulation stability may be increased by inclusion of an antimicrobial preservative. The PG-PUB of Applicant's specification at paragraph [0066] indicates that stability of the compositions may be increased by including an antimicrobial preservative to ensure the sterility of the compositions. Thus, the recited stability appears to be related to the fact that the claimed compositions are sterile and not to the recited particle size distribution or to any particular recited component. Because the prior art teaches the desirability of obtaining sterile formulations (Osbakken and Bernini), it is concluded that the formulations resulting from the combined prior art would necessarily exhibit the recited stability. It is also noted that neither Applicant's specification nor Applicant's arguments correlate the recited stability with the recited particle size distribution. Thus, the above conclusion about the prior art compositions necessarily exhibiting the required

stability is reasonable. Applicant is reminded that the Office lacks laboratory facilities to test the sterile prior art compositions to ascertain their stability. Thus, the burden is properly shifted to Applicant to demonstrate that the sterile formulations of the prior art do not exhibit the recited stability. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is proper.

Response to Arguments

Applicant's arguments filed June 29, 2010 have been fully considered but they are not persuasive. Applicant has traversed the instant rejection by attacking the references individually and arguing that none of the teachings of the prior art references teach, suggest, or render predictable (1) aqueous formulations comprising 0.04% to 0.06% w/w suspended solid fluticasone particles characterized by the recited particle size distribution, (2) aqueous formulations comprising 0.04% to 0.06% w/w suspended solid fluticasone particles in combination with an antifungal agent as recited in claim 1, (3) Applicant's claimed formulations exhibit surprising results and the Office has overlooked the statement in copending application 10/414,682 describing the comparison of Dey-FP with FLONASE® that Applicant's formulation exhibited an improvement in the magnitude of the TNSS; and (4) the prior art does not suggest compositions exhibiting the recited stability.

The Examiner respectfully disagrees with Applicant's traversal arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is acknowledged that the "ChemImage" data demonstrates that the particle size distribution of the commercially available FLONASE® product is not identical with the particles size distribution recited in Applicant's claims. However, this fact does not overcome the instant rejection as explained below. Regarding (1), it is conceded that FLONASE teaches an aqueous formulation comprising suspended solid fluticasone particles in an amount of 0.0375% w/w. However, it is noted that when the amount of fluticasone propionate taught by FLONASE® is reported to the same number of significant figures utilized in Applicant's claims for the amount of fluticasone, this amount would be 0.04% w/w. Therefore, it is reasonable to conclude that the amount of solid fluticasone particles present in FLONASE would exhibit the same or substantially similar physiological effects as the amount of solid fluticasone particles recited in Applicant's claims. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection, when the amount of suspended fluticasone particles taught by FLONASE® is compared with the amount recited in Applicant's claimed based on the same number of significant figures. MPEP § 2144.05. A prima facie obvious case of obviousness also exists when the prior art range is very close to the recited range, and the ordinary skilled artisan would reasonably expect both values to exhibit the same or substantially similar properties. MPEP § 2144.05.

Regarding (2) and the recited particle size distributions, it is the Examiner's position that optimization of particle sizes is routine in the field of inhalable formulations (i.e. both oral and

nasally administered) (Harris). Finding the optimal particle size and particle size distribution for a given particulate formulation is routinely practiced in the art (Harris) and as applied to the combined prior art, would reasonably be expected to yield the same or a substantially similar particle size distribution as claimed by Applicants. Thus, absent a showing of unexpected results, the instantly recited particle size distribution is not considered to represent non-obvious modification of the prior art, but rather merely the routine optimization of a known result effective parameter.

Applicant also emphasizes the fact that Osbakken focuses its teachings on solution formulations and droplet particle sizes suitable for nasal administration of a formulation to treat rhinosinusitis. For example, Osbakken teaches that the aerosolized anti-infective particles are surprisingly effective when they have a mass median aerodynamic diameter (MMAD) of about 1.0 to 5.0 microns [0081] and that the aerosolization/atomization of the formulations for nasal inhalation by a patient will result in liquid aerosol cloud particles having a MMAD of preferably between about 0.5 microns and 10 microns. The particle sizes identified by the prior art for nasal inhalation (Osbakken) overlap with the particle sizes recited in Applicant's claims. Applicant's arguments regarding Osbakken's teachings concerning solutions dismiss the fact that Osbakken explicitly teaches that the formulations can be in the form of suspensions. Applicant's arguments concerning Osbakken's alleged "preference for solutions" formulations are not a teaching away from obtaining aqueous suspensions. Thus, the appropriate particle sizes for targeting the nasal-paranasal mucosa were well known in the art, as evidenced by the teachings of the aforementioned combined prior art (Osbakken).

Regarding (3), it is unclear whether 50 mcg of fluticasone correlates with 0.04% w/w fluticasone or some other weight percentage. It is also noted that the data points are not displayed with error bars. The display of the uncertainty in the data points is deemed necessary because the data reported in Figures 1-4 are based upon a least squares mean analysis of the raw subjective Total Nasal Symptom Scores (TNSS) (i.e. these are aggregate data) manipulated using the ANOVA model. For this reason, wherein Applicants' data for the invented compositions and the prior art data points are very similar in magnitude, it would be reasonable for one to conclude that these data points are the same within a margin of error. As discussed above, the Applicant's data compared with the data for FLONASE® exhibit the same trends, fluctuations, are of a similar magnitude in the observed results, and in several instances yield the same experimental results (see, for example, data points at days 4, 5, 9, and 10).

Regarding (4), because the prior art teaches the desirability of obtaining sterile formulations (Osbakken and Bernini), it is concluded that the sterile formulations resulting from the combined prior art teachings would necessarily exhibit the recited stability. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is maintained.

Claims 71-74 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 445-446) in view of Bernini et al. (U.S.

Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Doi (U.S. Patent No. 6,368,616) and Meade (U.S. Patent No. 6,608,054).

Applicant Claims

Applicant claims a formulation as described above in the instant application further comprising a complexing agent (e.g. sodium edetate)

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, the DIH, Bernini, Harris, and Osbakken are set forth above.

Doi teaches aqueous suspensions for nasal application and that the compositions may contain additives which are broadly used in nasal drops, such as preservatives, buffers (e.g. **citric acid**), stabilizers, chelating agents (e.g. **citric acid and editic acid**), pH control agents (e.g. **citric acid**), etc. (title; abstract; col. 2, lines 61-65; col. 3, lines 8-17). The term "chelating agent" is synonymous with "complexing agent."

Meade teaches that sodium edetate and citric acid are known complexing agents (col. 9, lines 22-34).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions further comprising a complexing agent. This deficiency is cured by the teachings of Doi or Meade, which have been provided as supporting documents to show that complexing agents are conventional ingredients in aqueous nasal formulations.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a conventional additive broadly used in the formulation of nasal compositions, such as complexing agents. Regarding the specific complexing agent used, an ordinary skilled artisan would have been motivated to utilize any of the well-known complexing agents routinely utilized in aqueous nasal formulations (e.g. EDTA, sodium edetate, citric acid, etc.). An ordinary skilled artisan would have had a reasonable expectation of success, because the addition of complexing agents to aqueous formulations (e.g. nasally administrable aqueous suspensions) is conventional in the art. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 6/29/10 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by presenting the same and/or similar

arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

Claims 75-76 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Walker ("Management of allergic rhinitis", *Nursing Times,* 2003, *99(23)*, Abstract) and Hamuy et al.("Topical antiviral agents for herpes simplex virus infections," *Drugs Today*, 1998, *34(12)*, Abstract Only).

Applicant Claims

Applicant claims a formulation as described above in the instant application that additionally comprises a therapeutic amount of an antiviral agent selected from a group consisting essentially of acyclovir, famciclovir, valacyclovir, edoxudine, ganciclovir, foscarnet, cidovir (vistide), vitrasert, and formivirsen, and in some embodiments further comprises a complexing agent (e.g. sodium edetate).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE, the PDR®, the DIH, Bernini, Harris, and Osbakken are set forth above.

Walker teaches that viral and bacterial infection is the commonest acute cause of symptoms of allergic rhinitis (abstract).

Hamuy identifies several antiviral agents that have been used successfully to treat herpes simplex virus, including **cidofovir, edoxudine**, and penciclovir (abstract).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions comprising an antiviral agent and an antibacterial agent. The antibacterial agent deficiency is cured by the teachings of Osbakken (see Table 1). The antiviral agent deficiency is cured by the teachings of Walker and Hamuy, which have been provided as supporting documents to demonstrate that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are well-known anti-viral agents (Hamuy).

Finding of Prima Facie Obviousness Rational and Motivation *(MPEP §2142-2143)*

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a known antiviral agent, such as cidofovir or edoxudine, because viral infections are known to play a role in the etiology of allergic rhinitis and cidofovir, edoxudine, acyclovir, ganiciclovir, foscarnet, and formivirsen are well-known antiviral agents. An ordinary skilled artisan would

have had a reasonable expectation of success upon addition of a known antiviral agent, because viruses are known to play a role in the cause of acute allergic rhinitis and both cidofovir and edoxudine are known anti-viral agents. Regarding the particle size distributions recited in Applicant's claims, these have been addressed above in the previous rejections under 35 USC §103(a) and the relevant reasoning is incorporated herein by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 6/29/10 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by presenting the same and/or similar arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

Conclusion

Claims 1, 4-6, 10-12, 22-25, 27-30, 35, and 71-77 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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